Attorney Docket No. 01626C/HG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of	:	Takashi FUJITA et al.
Serial No.	:	09/991,100
Filed	:	November 21, 2001
For	:	
Art Unit	:	1626
Examiner	:	Laura Lynne Stockton

DECLARATION UNDER 37 CFR 1.132

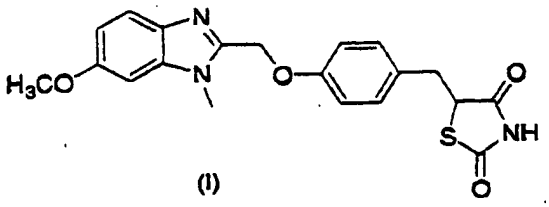
Dr. Kazushi ARAKI declares that he obtained his D.V.M. degree in Veterinary medicine from Tokyo University of Agriculture and Technology in 1992 and obtained his Ph.D. in 1996 from Tokyo University. His Ph.D. research was Meiotic abnormalities of c-mos knockout mouse oocytes : activation after first meiosis or entrance into third meiotic metaphase.

He joined Sankyo in 1996. He is now an Associate Chief Researcher in Pharmacology & Molecular Biology res. labs. in Sankyo. His research interests are antidiabetic mechanism of insulin sensitizer in diabetic animal model; characterization of diabetic animal models and pharmacology of antidiabetic drugs.

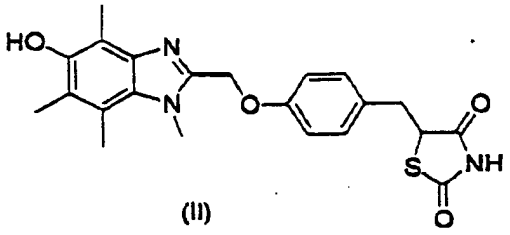
In order to show the unexpectedly high activity of the claimed compounds and compositions when used in the claimed methods, additional comparative data was obtained under his

supervision and control. This data is presented in the following:

Test compounds
We use four compounds for this comparative test.



(I)



(II)

In the case of the compounds of formula (I), its hydrochloride salt and free form are called Compound A and Compound B respectively. Compound A is the hydrochloride salt claimed in this application.

And in the case of the compounds of formula (II), its hydrochloride salt and free form are called Compound C and Compound D respectively. Compound C and D are from the cited USP No. 5,886,014 and these are disclosed with physical properties. (Compound C is Example 4 and Compound D is Example 3 in the patent.)

One of the reasons why Compound C and D were chosen for comparison is that Compound C is the only hydrochloride compound

prepared in USP 5,886,014. And the other reason is that the structure of those compounds is similar to that of Compound A. For example, the structural difference of the comparative Compound C and D from Compound A is only at the substituent groups on the benzimidazole moiety.

Test Methods

The comparison was made of hypoglycemic activity. (This test method is not same as mentioned in the present application.)

Comparative Test Example

Hypoglycemic action

The blood sample was collected from the tail vein of each KK mouse (4-5 month old) which developed diabetes and its plasma glucose level was measured after centrifugation. These mice were then classified into groups (4 mice per group). For three days, powdered food (F-2, Funabashi Farm) that adjusted to contain the test compound at concentrations of 0.0001%(compound A or B) or 0.001%(compound C or D) was administered to mice. The concentrations were arranged that the average plasma glucose level of free form compounds administered group would be shown almost the same. The mouse group to which the test compound was administered refers to "the medicine administered group", while

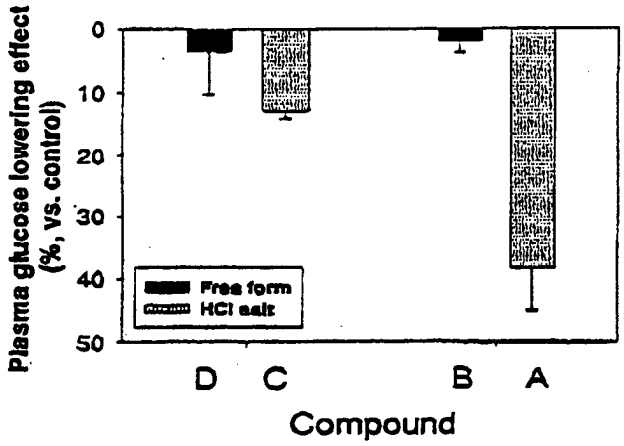
that to which the powdered food free of the test compound was administered refers to "the control". After three days, the blood sample was collected from the tail vein of each of the mouse and the plasma glucose concentration was measured by a glucose analyzer ("Glucoloader-GXT", A&T Inc.). The plasma glucose lowering rate was calculated from the following equation:

Plasma glucose lowering rate (%)=

(average plasma glucose level of the control-average plasma glucose level of the medicine administered group) X 100/the plasma glucose level of the control

Comparative Test Results

The comparative biological test data are as shown below.



Discussion

To establish the expectation in the art, the following is noted:

In the Fujita et al. patent, there is a data for Compound C that shows nearly two times stronger activity than its free form compound D in plasma glucose lowering rate (Refer to Table 6 of USP 5,886,014). Also at the above comparative test results, Compound C shows nearly three times stronger activity than its free form Compound D.

Further to above information, Berg et al. teach that it could be generally expected to prepare the salt of known compounds with increasing physicochemical properties such as solubility and hygroscopicity. Berg et al., however, does not specifically teach or suggest an improving activity effect that would be expected from hydrochloride salt of the known compounds such as the compounds within the scope of USP 5,886,014.

In consideration of above knowledge obtained from above reference and comparative data of Compound C, it is submitted that one skilled in the art at the time of invention would expect the parent compounds within the patent nearly two to three times activity improving effect from their hydrochloride salts as compared with the free compound.

The actual results are about an order of magnitude greater than the "expectation." The activity of Compound A is about twenty times greater than that of its free form compound B as shown by comparative test results. This effect of hydrochloride salt is far stronger than that would have been expected for this kind of compounds, in consideration of above mentioned reference and common knowledge. Therefore one skilled in the art at the time of the invention would not have expected this effect of the salt.

In conclusion, Compound A shows an unexpected activity improving effect compared to the compounds within the broad scope of the reference patent, so the invention of the hydrochloride salt claimed herein is a selection invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: March 11, 2003

Kazushi Araki

Kazushi ARAKI